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Letter to the Editor

Phenotypic Discordance in a Family With Monozygotic Twins and Non-Syndromic Cleft Lip and Palate

To the Editor:

Despite considerable research, the cause of non-syndromic cleft lip with or without cleft palate (NSCLP) is still an enigma. Case-control and cohort studies have searched for environmental factors that might influence the development of this common malformation, such as maternal cigarette smoking [Saxén, 1974; Evans et al., 1979; Ericson et al., 1979; Shiono et al., 1986; Khoury et al., 1987, 1989; Werler et al., 1990; Hwang et al., 1995], periconceptional supplementation of folic acid and multivitamins [Tolarová and Harris, 1995; Shaw et al., 1995], agricultural chemical use [Gordon and Shy, 1981; Nurminen et al., 1995], and place of residence [Christensen et al., 1995], among others. However, these studies are subject to numerous biases [Khoury et al., 1992; Hemminki et al., 1995; Nurminen, 1995; Lie, 1995], and their results have often been contradictory and inconclusive.

There is a well-known genetic component to the cause of NSCLP, but its specific nature remains uncertain [Juriloff, 1993]. Researchers performing complex segregation analyses have proposed a single gene of major effect for NSCLP, with autosomal recessive [Chung et al., 1986; Marazita et al., 1992], or dominant [DePaepe, 1989; Temple et al., 1989; Hecht et al., 1990; Ray et al., 1993] inheritance, but always with incomplete penetrance. Several groups are currently engaged in linkage studies intended to identify major gene[s] for NSCLP. Various candidate regions have been reported to show linkage or allelic association with NSCLP: F13A on chromosome 6 [Eiberg et al., 1987], transforming growth factor-alpha [TGFα] on chromosome 2 [Ardinger et al., 1989], retinoic acid receptor-alpha [RARα] on chromosome 17 [Chenevix-Trench et al., 1992], MFD38 on chromosome 4 [Beiraghi et al., 1994], chromosomal region 6p24 [Davies et al., 1995], and BCL3 on chromosome 19 [Stein et al., 1995]. The lack of support by other studies [Hecht et al., 1991, 1993; Vintiner et al., 1992] has been addressed in detail by Farrall et al. [1993] and Murray [1995].

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CLINICAL REPORT

Here we present a clinical case to generate interest in studies of recurrence risk for discordant MZ twins for CL/P, an area still unexplored in the literature. In 1994, as part of a linkage study, we met a NSCLP family with two affected members (Fig. 1). The propositus, individual 8, was diagnosed by a medical geneticist as having a right cleft lip (CL) and a complete cleft palate (CP). The uvula was intact. The child was the product of an uncomplicated pregnancy, and his mother reported no exposure to teratogens during the first trimester of gestation. Multivitamin supplements were taken between the second and fifth months of pregnancy. Maternal and paternal age at time of delivery were 27 and 26 years, respectively. Birth and development were uncomplicated. The patient's mother and aunt are identical twins. His mother, individual 4 in Figure 1, was diagnosed as having a left CL with a complete CP. No uvula was present. Her sister, individual 5, was born with no oral cleft and an intact uvula. Review of the obstetric charts from this twin pregnancy showed no complications. Individual 7, brother of the twin sisters, had an isolated syndactyly between the third and fourth finger in one hand, enough to prevent wearing a ring, but this individual was otherwise normal.

In addition to the high degree of physical resemblance between the twins, monozygozity was confirmed by polymerase chain reaction (PCR) amplification and analysis of six polymorphic markers on different chromosomes [Eufinger et al., 1995] (data available upon request). The patient's mother and aunt had perfect agreement for all six markers.

Cases of MZ twins discordant for genetically determined disorders have been reported, e.g., Ullrich-Turner syndrome or Duchenne muscular dystrophy [Eufinger et al., 1993]. In these cases postzygotic mitotic nondisjunction or anaphase lags, as well as uneven X-chromosome inactivation are possible explanations [Gonsoulin et al., 1990; Perlman et al., 1990; Lupski et al., 1991]. Previous twin studies of NSCLP have reported concordance rates of 36% (range 33–78) for MZ twins and 1% [range 0–14.3] for DZ twins [Eufinger et al., 1993]. As MZ twins possess identical genomes, discordance or differing grades of clefting may be explained by exposure to potential teratogenic agents (i.e., respiratory viruses [Zhang and Cai, 1993]), a postzygotic mutation, or the effect of chance. This family is particularly interesting, since the affected MZ twin gave birth to an affected child, thus making in

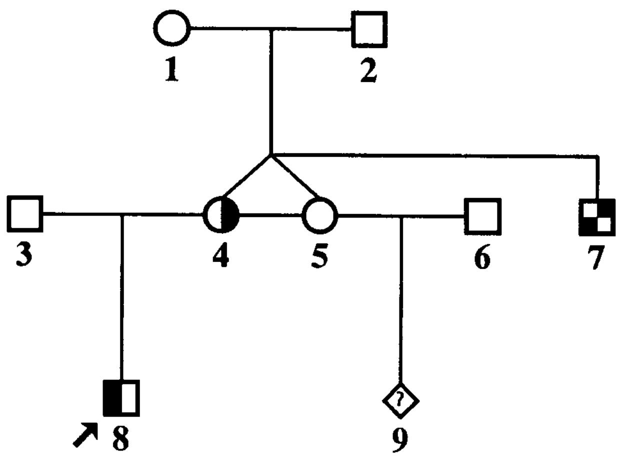

Fig. 1. Pedigree of family 40. Individual 4 has a left cleft lip (CL) and a complete cleft palate (CP). Individual 8, the proband, has a right CL and a complete CP. Individual 7 has a webbed finger in a hand but he is otherwise normal.

utero environmental factors unlikely to be solely responsible for the genesis of these oral clefts. This raises the question of how best to counsel the unaffected sister (individual 5 in Fig. 1) as to her risk of having a child with a NSCLP: "Is it the same as her identical twin's risk (approximately 8–10 times higher than the risk of the general population) or lower (3–5 times), as she herself is 'unaffected'?" The risk for the unaffected sister to have a child with CL/P was given as 3–10% (potentially as high as that for her affected sister, though likely to be less). This estimate has been debated by other geneticists. While this family is being followed, additional twin studies, including families like the one presented here, may provide more appropriate estimates of risk.

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